Selenium containing heterocyclic: Synthesis, antimicrobial of some new selenazole Substituted phthalazin-ones

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Abstract: The principal purpose of the present study is to synthesize and investigate the antimicrobial and antifungal activities of new 1, 3-selenazole derivatives having phthalazin-1(2H)-one moieties. A multi-step reaction route was developed to synthesize a several of targeted derivatives starting from 4-alkyl/aryl-phthalazin-1(2H)-one and 2-chloro-N-phenylacetamide. The structures of the synthesized compounds were confirmed by ^{1}HNMR, ^{13}CNMR, MS, IR spectroscopy and by elemental analysis. The antimicrobial and antifungal activities of all derivatives against four species of bacteria and two species of fungi were investigated. The antimicrobial and antifungal activity was determined in the extracts using disk diffusion method. Amoxicillin and Ketoconazole were used as standard drugs for the bacteria and fungi, respectively.
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1. Introduction

Heterocyclic compounds with nitrogen containing the largest part of chemical existance, which are part of several natural products, fine chemicals, and biologically active pharmaceuticals. Phthalazin-1(2H)-one derivatives are of considerable interest due to their antidiabetic [1], antiallergic [2], vasorelaxant [3], PDE4 inhibitors [4], VEGF (vascular endothelial growth factor) receptor tyrosine kinases for the treatment of cancer [5], antiasthmatic agents [6], herbicidal [7] like activities. A number of established drug molecules like Hydralazine [8], Budralazine [9], Azelastine [10], Ponalrestat [11] and Zopolrestat [12] were prepared from the corresponding phthalazinones. On the other hand, the introduction of selenium into organic molecules often permits modification of their chemical properties and biological activities [13-14]. The unique biochemical and pharmaceutical properties of organo selenium compounds make them very attractive, especially for bioorganic and medicinal chemists. These compounds; Se-containing heterocycles, have gained great importance over the last 25 years. Among a large variety of Se-containing heterocycles, heterocycles containing the 1, 3-selenazoles moiety are of interest due to their pharmacological and biological activities [15]. Several reviews [16] describe their preparation [17] and pharmaceutical potential [18]. Most researchers have been focused on their uses as anticancer [19] and anti-radiation agents [20], as protein kinase activators [21], and as superoxide anion scavengers [22]. The diverse biological activities of phthalazin-1(2H)-one, and 1, 3- selenazoles pharmacophores envisaged us to plan a new lead compounds that may exhibit wide pharmacological activities. By combining these pharmacophore components in a molecule to give a compact system, we designed and synthesized a series of phthalazin-1(2H)-one derivatives containing 1, 3-selenazole moieties.

2. Experimental

Melting points were determined on a MEL-TEMP II melting point apparatus in open glass capillaries and are uncorrected. The infrared spectra IR were recorded for potassium bromide disks on a Pye-Unicam SP1025 spectrophotometer. NMR spectra were obtained at ambient temperature (~25 ◦ C) with a Bruker AC-250 spectrometer or with a Varian Gemini 200 spectrometer at 250 MHz using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were obtained on a Hewlett-Packard 5995 gas chromatography-mass spectrometer system or on a Shimadzu GCMS-QP 1000 EX mass spectrometer. Homogeneity of the products and follow up of the reactions were checked

by ascending thin-layer chromatography TLC on plates precoated with silica gel G (E. Merck; layer thickness 0.25 mm), used without pretreatment.

General procedure for preparation of 2-(1-oxo-4-substituted-phthalazin-2(1H)-yl)-N-phenylacetamide (3a-j)

A mixture of phthalazinone derivative 2 (0.01 mol), 2-chloro-N-phenylacetamide (0.03 mol) and potassium carbonate (4.1 g, 0.03 mol) in 30 mL dry acetone was heated under reflux for 30 h, cooled at room temperature and poured into water. The obtained solid was filtered off and crystallized from petroleum ether 40–60 ºC to give 3.

2-(1-Oxo-4-phenylphthalazin-2(1H)-yl)-N-phenylacetamide (3a).

M.p.161–162 ºC; yield 96%; 1H NMR (DMSO-d6) δ: 4.33 (s, 2H, CH2), 6.98 (s, 1H, NH exchangeable with D2O), 7.07–8.21 (m, 14H, Ar–H); IR (KBr) v: 3260, 1670, 1655 cm-1; MS (70 eV) m/z (%):355 (M+, 16). Anal. calcd. For C22H17N3O2: C, 74.35; H, 4.82; N, 11.82; found C C, 74.30; H, 4.89; N, 11.80.

2-(1-Oxo-4-(4-methoxyphenyl) phthalazin-2(1H)-yl)-N-phenylacetamide (3b).

M.p.153–154 ºC; yield 87%; 1H NMR (DMSO-d6) δ: 4.12 (s, 3H, OCH3), 4.38 (s, 2H, CH2), 7.01 (s, 1H, NH exchangeable with D2O), 7.11–8.14 (m, 13H, Ar–H); IR (KBr) v: 3218, 1678, 1650 cm-1; MS (70 eV) m/z (%):385 (M+, 33). Anal. calcd. For C23H19N3O3: C, 71.67; H, 4.97; N, 10.90; found C, 71.61; H, 4.99; N, 10.95.

2-(1-Oxo-4-(4-chlorophenyl) phthalazin-2(1H)-yl)-N-phenylacetamide (3c).

M.p.150–151 ºC; yield 93%; 1H NMR (DMSO-d6) δ: 4.40 (s, 2H, CH2), 6.97 (s, 1H, NH exchangeable with D2O), 7.10–8.16 (m, 13H, Ar–H); IR (KBr) v: 3310, 1674, 1651 cm-1; MS (70 eV) m/z (%):389 (M+, 21). Anal. calcd. For C22H16ClN3O2: C, 67.78; H, 4.14; Cl, 9.09; found C, 67.81; H, 4.11; Cl, 9.10.

2-(1-Oxo-4-(3, 4-dichlorophenyl) phthalazin-2(1H)-yl)-N-phenylacetamide (3d).

M.p.129–130 ºC; yield 91%; 1H NMR (DMSO-d6) δ: 4.43 (s, 2H, CH2), 7.09 (s, 1H, NH exchangeable with D2O), 7.15–8.20 (m, 12H, Ar–H); IR (KBr) v: 3254, 1678, 1657 cm-1; MS (70 eV) m/z (%):423 (M+, 19). Anal. calcd. For C22H15Cl2N3O2: C, 62.28; H, 3.56; Cl, 16.71; N, 9.90; found C, 62.23; H, 3.59; Cl, 16.71; N, 9.97.

2-(1-Oxo-4-(4-chlorobenzyl) phenyl) phthalazin-2(1H)-yl)-N-phenylacetamide (3e).

M.p.144–145 ºC; yield 89%; 1H NMR (DMSO-d6) δ: 4.25 (s, 2H, CH2), 4.43 (s, 2H, CH2), 6.90 (s, 1H, NH exchangeable with D2O), 7.05–8.27 (m, 17H, Ar–H); IR (KBr) v: 3199, 1673, 1659 cm-1; MS (70 eV) m/z (%):479 (M+, 10). Anal. calcd. For C29H22ClN3O2: C, 72.57; H, 4.62; Cl, 7.39; N, 8.75; found C, 72.50; H, 4.68; Cl, 7.36; N, 8.79.

2-(1-Oxo-4-(3-chloro-4-methylphenyl) phenyl) phthalazin-2(1H)-yl)-N-phenylacetamide (3f).

M.p.158–159 ºC; yield 97%; 1H NMR (DMSO-d6) δ: 2.44 (s, 3H, CH3), 4.46 (s, 2H, CH2), 6.99 (s, 1H, NH exchangeable with D2O), 7.10–8.26 (m, 12H, Ar–H); IR (KBr) v: 3287, 1677, 1653 cm-1; MS (70 eV) m/z (%):403 (M+, 24). Anal. calcd. For C23H18ClN3O2: C, 68.40; H, 4.49; Cl, 8.78; N, 10.40; found C, 68.44; H, 4.52; Cl, 8.70; N, 10.45.

2-(1-Oxo-4-(2, 4, 6-trimethylphenyl) phenyl) phthalazin-2(1H)-yl)-N-phenylacetamide (3g).

M.p.120–121 ºC; yield 95%; 1H NMR (DMSO-d6) δ: 2.36 (s, 3H, CH3), 2.48 (s, 6H, 2CH3), 4.33 (s, 2H, CH2), 7.01 (s, 1H, NH exchangeable with D2O), 7.11–8.27 (m, 11H, Ar–H); IR (KBr) v: 3264, 1679, 1650 cm-1; MS (70 eV) m/z (%):397 (M+, 9). Anal. calcd. For C25H23N3O2: C, 75.54; H, 5.83; N, 10.57; found C, 75.58; H, 5.81; N, 10.50.

2-(1-Oxo-4-(4-benzylphenyl) phenyl) phthalazin-2(1H)-yl)-N-phenylacetamide (3h).

M.p.133–134 ºC; yield 88%; 1H NMR (DMSO-d6) δ: 4.26 (s, 2H, CH2), 4.41 (s, 2H, CH2), 6.96 (s, 1H, NH exchangeable with D2O), 7.08–8.25 (m, 18H, Ar–H); IR (KBr) v: 3265, 1671, 1654 cm-1; MS (70 eV) m/z (%):445 (M+, 8). Anal. calcd. For C29H23N3O2: C, 78.18; H, 5.20; N, 9.43; found C, 78.12; H, 5.27; N, 9.40.

2-(1-Oxo-4-(4-(pyridin-4-ylmethyl) phenyl) phthalazin-2(1H)-yl)-N-phenylacetamide (3i)

M.p.141–142 ºC; yield 90%; 1H NMR (DMSO-d6) δ: 4.06 (s, 2H, CH2), 4.91 (s, 2H, CH2), 6.98 (s, 1H, NH exchangeable with D2O), 7.04–8.68 (m, 17H, Ar–H and pyridine protons); IR (KBr) v: 3294, 1677 and 1653 cm-1; MS (70 eV) m/z (%):446 (M+, 13). Anal. calcd. For C28H22N4O2: C, 75.32; H, 4.97; N, 12.55; found C, 75.36; H, 4.92; N, 12.59.

2-(1-Oxo-4-(biphenyl-4-yl) phenyl) phthalazin-2(1H)-yl)-N-phenylacetamide (3j).

M.p.156–157 ºC; yield 94%; 1H NMR (DMSO-d6) δ: 4.49 (s, 2H, CH2), 7.00 (s, 1H, NH exchangeable with D2O), 7.09–8.28 (m, 18H, Ar–H); IR (KBr) v: 1678 and 1653 cm-1; MS (70 eV) m/z (%):431 (M+, 20). Anal. calcd. For C28H21N3O2: C, 77.94; H, 4.91; N, 9.74; found C, 78.00; H, 4.90; N, 9.71.

General procedure for preparation of 2-(1-oxo-4-substituted-phthalazin-2(1H)-yl)-N-phenylacetimidoyl chloride (4a-j)

A mixture of N-phenylacetamide derivative of type 3 and 2-3 equiv. SOCl2 was heated to reflux for 2-3 h, until the evolution of SO2 ceased. Excess SOCl2 was evaporated, and the corresponding N-

phenylacetimidoyl chloride 4 was obtained as a white solid, which was dried in vacuo for 24 h.

2-(1-Oxo-4-phenylphthalazin-2(1H)-yl)-N-phenylacetimidoyl chloride (4a).

M.p.130–131 ºC; yield 77%; 1H NMR (DMSO-d6) δ: 3.65 (s, 2H, CH2), 7.04–8.20 (m, 14H, Ar–H); 13C NMR (DMSO-d6) δ: 52.1(CH2), 123.2, 123.2, 126.0, 127.7, 128.0, 129.1, 129.7, 130.1, 130.8, 132.1, 132.7, 133.1, 133.8, 135.9, 139.2(CN2), 153.4, 160.4(CO); IR (KBr) v: 1671, 1611 cm-1; MS (70 eV) m/z (%):373 (M+, 11). Anal. calcd. For C22H16ClN3O: C, 70.68; H, 4.31; Cl, 9.48; N, 11.24; found C, 70.61; H, 4.33; Cl, 9.42; N, 11.29.

2-(1-Oxo-4-(4-methoxyphenyl) phthalazin-2(1H)-yl)-N-phenylacetimidoyl chloride (4b).

M.p.110–111 ºC; yield 72%; 1H NMR (DMSO-d6) δ: 3.51 (s, 2H, CH2), 4.10 (s, 3H, OCH3), 7.10–8.21 (m, 13H, Ar–H); 13C NMR (DMSO-d6) δ: 50.2(CH2), 58.1(OCH3), 116.4, 122.9, 123.9, 125.7, 126.7, 128.0, 128.3, 129.3, 130.7, 131.5, 132.6, 133.2, 135.4, 138.4(CN2), 150.4, 160.5, 162.0; IR (KBr) v: 1678, 1610 cm-1; MS (70 eV) m/z (%):403 (M+, 7). Anal. calcd. For C23H18ClN3O2: C, 68.40; H, 4.49; Cl, 8.78; N, 10.40; found C, 68.46; H, 4.45; Cl, 8.74; N, 10.34.

2-(1-Oxo-4-(4-chlorophenyl) phthalazin-2(1H)-yl)-N-phenylacetimidoyl chloride (4c).

M.p.103–104 ºC; yield 65%; 1H NMR (DMSO-d6) δ: 3.95 (s, 2H, CH2), 7.12–8.20 (m, 13H, Ar–H); 13C NMR (DMSO-d6) δ: 52.1(CH2), 122.8, 123.2, 126.7, 126.6, 127.6, 128.3, 129.0, 130.3, 130.9, 131.8, 132.0, 132.8, 135.3, 137.5, 139.2 (CN2), 150.9, 160.0(CO); IR (KBr) v: 1674, 1613 cm-1; MS (70 eV) m/z (%):408 (M+, 18). Anal. calcd. For C22H15Cl2N3O: C, 64.72; H, 3.70; Cl, 17.37; N, 10.29; found C, 64.70; H, 3.77; Cl, 17.32; N, 10.33.

2-(1-Oxo-4-(3, 4-dichlorophenyl) phthalazin-2(1H)-yl)-N-phenylacetimidoyl chloride (4d).

M.p.95–96 ºC; yield 70%; 1H NMR (DMSO-d6) δ: 4.07 (s, 2H, CH2), 7.10–8.22 (m, 12H, Ar–H); 13C NMR (DMSO-d6) δ: 50.1 (CH2), 123.0, 123.6, 126.7, 127.0, 128.6, 129.5, 130.2, 131.2, 131.7, 132.3, 132.9, 133.2, 133.9, 134.6, 135.4, 136.3, 139.7 (CN2), 150.6, 159.6(CO); IR (KBr) v: 1678, 1618 cm-1; MS (70 eV) m/z (%):442 (M+, 4). Anal. calcd. For C22H14Cl3N3O: C, 59.68; H, 3.19; Cl, 24.02; N, 9.49; found C, 59.70; H, 3.14; Cl, 24.06; N, 9.51.

2-(1-Oxo-4-(4-(4-chlorobenzyl) phenyl) phthalazin-2(1H)-yl)-N-phenylacetimidoyl chloride (4e). M.p.100–101 ºC; yield 68%; 1H NMR (DMSO-d6) δ: 3.85 (s, 2H, CH2), 4.43 (s, 2H, CH2), 7.06–8.25 (m, 17H, Ar–H); IR (KBr) v: 1673, 1611 cm-1; MS (70 eV) m/z (%):498 (M+, 12). Anal. calcd. For C29H21Cl2N3O: C, 69.89; H, 4.25; Cl, 14.23; N, 8.43; found C, 69.94; H, 4.20; Cl, 14.20; N, 8.49.

2-(1-Oxo-4-(3-chloro-4-methylphenyl) phthalazin-2(1H)-yl)-N-phenylacetimidoyl chloride (4f).

M.p.113–114 ºC; yield 66%; 1H NMR (DMSO-d6) δ: 2.44 (s, 3H, CH3), 3.88 (s, 2H, CH2), 7.08–8.21 (m, 12H, Ar–H); IR (KBr) v: 1677, 1613 cm-1; MS (70 eV) m/z (%):422 (M+, 7). Anal. calcd. For C23H17Cl2N3O: C, 65.41; H, 4.06; Cl, 16.79; N, 9.95; found C, 65.46; H, 4.01; Cl, 16.73; N, 9.98.

2-(1-Oxo-4-(2, 4, 6-trimethylphenyl) phthalazin-2(1H)-yl)-N-phenylacetimidoyl chloride (4g).

M.p.98–99 ºC; yield 75%; 1H NMR (DMSO-d6, 300 MHz) δ: 2.36 (s, 3H, CH3), 2.48 (s, 6H, 2CH3), 4.03 (s, 2H, CH2), 7.08–8.25 (m, 11H, Ar–H); IR (KBr) v: 1679, 1614 cm-1; MS (70 eV) m/z (%):415 (M+, 6). Anal. calcd. For C25H22ClN3O: C, 72.19; H, 5.33; Cl, 8.52; N, 10.10; found C, 72.25; H, 5.30; Cl, 8.57; N, 10.16.

2-(1-Oxo-4-(4-benzylphenyl) phthalazin-2(1H)-yl)-N-phenylacetimidoyl chloride (4h).

M.p.91–92 ºC; yield 71%; 1H NMR (DMSO-d6) δ: 3.84 (s, 2H, CH2), 4.47 (s, 2H, CH2), 7.08–8.28 (m, 18H, Ar–H); IR (KBr) v: 1671 and 1614 cm-1; MS (70 eV) m/z (%):463 (M+, 15), 305 (100). Anal. calcd. For C29H22ClN3O: C, 75.07; H, 4.78; Cl, 7.64; N, 9.06; found C, 75.11; H, 4.72; Cl, 7.67; N, 9.00.

2-(1-Oxo-4-(4-(pyridin-4-ylmethyl) phenyl) phthalazin-2(1H)-yl)-N-phenylacetimidoyl chloride (4i)

M.p.112–113 ºC; yield 64%; 1H NMR (DMSO-d6) δ: 4.06 (s, 2H, CH2), 4.90 (s, 2H, CH2), 7.05–8.64 (m, 17H, Ar–H and pyridine protons); IR (KBr) v: 1677, 1613 cm-1; MS (70 eV) m/z (%):464 (M+, 5). Anal. calcd. For C28H21ClN4O: C, 72.33; H, 4.55; Cl, 7.63; N, 12.05; found C, 72.35; H, 4.50; Cl, 7.69; N, 12.10.

2-(1-Oxo-4-(biphenyl-4-yl) phthalazin-2(1H)-yl)-N-phenylacetimidoyl chloride (4j).

M.p.121–122 ºC; yield 60%; 1H NMR (DMSO-d6) δ: 3.79 (s, 2H, CH2), 7.07–8.25 (m, 18H, Ar–H); IR (KBr) v: 1678, 1610 cm-1; MS (70 eV) m/z (%):449 (M+, 14). Anal. calcd. For C28H20ClN3O: C, 74.74; H, 4.48; Cl, 7.88; N, 9.34; found C, 74.78; H, 4.41; Cl, 7.82; N, 9.39.

General procedure for preparation of 2-(1-oxo-4-substituted-phthalazin-2(1H)-yl)-N'-phenylacetimidoyl isoselenocyanate (5a-j).

A freshly prepared solution of KSeCN in acetone was added to 4 under stirring. Shortly after all 4 had been dissolved, the yellowish phenylacetimidoyl isoselenocyanate 5 crystallized from the solution. The mixture was poured on ice/water under stirring and the product was filtered by suction and air-dried.

2-(1-Oxo-4-phenylphthalazin-2(1H)-yl)-N'-phenylacetimidoyl isoselenocyanate (5a).

M.p.80–81 ºC; yield 78%; 1H NMR (DMSO-d6) δ: 3.60 (s, 2H, CH2), 7.03–8.20 (m, 14H, Ar–H); 13C NMR (DMSO-d6) δ: 56.3(CH2), 122.4, 123.8, 126.7, 127.4, 127.9, 129.0, 129.8, 130.3, 130.9, 132.2, 132.8, 133.0, 133.9, 135.6, 138.2(CN2), 140.2(NCSe), 150.1, 160.1(CO); IR (KBr) v: 1988, 1672, 1615 cm-1; MS (70 eV) m/z (%):444 (M+1, 100). Anal. calcd. For C23H16N4OSe: C, 62.31; H, 3.64; N, 12.64; found C, 62.30; H, 3.69; N, 12.61.

2-(1-Oxo-4-(4-methoxyphenyl) phthalazin-2(1H)-yl)-N'-phenylacetimidoyl isoselenocyanate (5b). M.p.91–925 ºC; yield 68%; 1H NMR (DMSO-d6) δ: 3.56 (s, 2H, CH2), 4.11 (s, 3H, OCH3), 7.15–8.24 (m, 13H, Ar–H); 13C NMR (DMSO-d6) δ: 52.2(CH2), 59.1(OCH3), 115.9, 122.7, 123.8, 125.5, 126.0, 127.0, 128.3, 129.9, 130.5, 131.2, 132.6, 133.1, 135.1, 138.4(CN2), 140.4(NCSe), 150.1, 160.1, 162.9; IR (KBr) v: 1980, 1676, 1617 cm-1; MS (70 eV) m/z (%):474 (M+1, 100). Anal. calcd. For C24H18N4O2Se: C, 60.89; H, 3.83; N, 11.84; found C, 60.83; H, 3.85; N, 11.88.

2-(1-Oxo-4-(4-chlorophenyl) phthalazin-2(1H)-yl)-N'-phenylacetimidoyl isoselenocyanate (5c). M.p.83–84 ºC; yield 85%; 1H NMR (DMSO-d6) δ: 3.95 (s, 2H, CH2), 7.12–8.20 (m, 13H, Ar–H); 13C NMR (DMSO-d6) δ: 50.0(CH2), 122.5, 123.0, 126.1, 126.9, 127.3, 128.0, 129.2, 130.1, 130.9, 131.4, 132.0, 132.9, 135.1, 137.2, 139.1 (CN2), 140.0(NCSe), 150.8, 160.5(CO); IR (KBr) v: 2000, 1674, 1616 cm-1;MS (70 eV) m/z (%):477 (M+, 10). Anal. calcd. For C23H15ClN4OSe: C, 57.82; H, 3.16; Cl, 7.42; N, 11.73; found C, 57.88; H, 3.11; Cl, 7.42; N, 11.77.

2-(1-Oxo-4-(3, 4-dichlorophenyl) phthalazin-2(1H)-yl)-N'-phenylacetimidoyl isoselenocyanate (5d). M.p.71–72 ºC; yield 72%; 1H NMR (DMSO-d6) δ: 4.05 (s, 2H, CH2), 7.10–8.27 (m, 12H, Ar–H); 13C NMR (DMSO-d6) δ: 55.1 (CH2), 122.7, 123.6, 126.4, 127.8, 128.1, 129.1, 130.1, 131.2, 131.7, 132.2, 132.9, 133.0, 133.9, 134.1, 135.7, 136.2, 138.1 (CN2), 140.6(NCSe), 150.0, 159.1(CO); IR (KBr) v: 2050, 1675, 1617 cm-1; MS (70 eV) m/z (%):512 (M+, 13). Anal. calcd. For C23H14Cl2N4OSe: C, 53.93; H, 2.75; Cl, 13.84; N, 10.94; found C, 53.99; H, 2.73; Cl, 13.84; N, 10.9.

2-(1-Oxo-4-(4-(4-chlorobenzyl) phenyl) phthalazin-2(1H)-yl)-N'-phenylacetimidoyl isoselenocyanate (5e)

M.p.82–83 ºC; yield 81%; 1H NMR (DMSO-d6) δ: 3.80 (s, 2H, CH2), 4.41 (s, 2H, CH2), 7.05–8.25 (m, 17H, Ar–H); 13C NMR (DMSO-d6) δ: 42.5, (CH2), 55.1 (CH2), 122.6, 124.1, 125.2, 127.0, 127.6, 128.2, 129.0, 129.9, 130.1, 130.5, 130.8, 131.2, 131.4, 131.9, 132.0, 132.6, 138.3 (CN2), 139.1, 140.4(NCSe), 144.2, 150.5, 159.7(CO); IR (KBr) v: 2013, 1673, 1618 cm-1; MS (70 eV) m/z (%):567 (M+, 8). Anal. calcd. For C30H21ClN4OSe: C, 63.44; H, 3.73; Cl, 6.24; N, 9.87; found C, 63.40; H, 3.78; Cl, 6.24; N, 9.80.

2-(1-Oxo-4-(3-chloro-4-methylphenyl) phthalazin-2(1H)-yl)-N'-phenylacetimidoyl isoselenocyanate (5f).

M.p.90–91 ºC; yield 79%; 1H NMR (DMSO-d6) δ: 2.46 (s, 3H, CH3), 3.89 (s, 2H, CH2), 7.07–8.28 (m, 12H, Ar–H); 13C NMR (DMSO-d6) δ: 20.2(CH3), 45.1, (CH2), 120.2, 122.5, 123.0, 125.1, 126.9, 127.4, 127.9, 128.4, 129.9, 130.3, 131.0, 131.8, 132.4, 133.0, 134.1, 137.2, 139.1 (CN2), 141.4(NCSe), 151.5, 159.9(CO); IR (KBr) v: 1998, 1670, 1616 cm-1; MS (70 eV) m/z (%):491 (M+, 5). Anal. calcd. For C24H17ClN4OSe: C, 58.61; H, 3.48; Cl, 7.21; N, 11.39; found C, 58.61; H, 3.47; Cl, 7.21; N, 11.42.

2-(1-Oxo-4-(2, 4, 6-trimethylphenyl) phthalazin-2(1H)-yl)-N'-phenylacetimidoyl isoselenocyanate (5g).

M.p.64–65 ºC; yield 78%; 1H NMR (DMSO-d6) δ: 2.35 (s, 3H, CH3), 2.50 (s, 6H, 2CH3), 4.06 (s, 2H, CH2), 7.08–8.29 (m, 11H, Ar–H); 13C NMR (DMSO-d6) δ: 20.6(CH3), 21.8(2CH3), 46.2, (CH2), 121.1, 122.5, 126.0, 126.8, 127.1, 128.4, 129.5, 130.1, 130.4, 132.0, 132.3, 135.1, 157.2, 139.0(CN2), 140.8(NCSe), 142.5, 150.9,160.6(CO); IR (KBr) v: 1679, 1618 cm-1; MS (70 eV) m/z (%):486 (M+1, 17). Anal. calcd. For C26H22N4OSe: C, 64.33; H, 4.57; N, 11.54; found C, 64.31; H, 4.59; N, 11.52.

2-(1-Oxo-4-(4-benzylphenyl) phthalazin-2(1H)-yl)-N'-phenylacetimidoyl isoselenocyanate (5h)

M.p.79–80 ºC; yield 68%; 1H NMR (DMSO-d6, 300 MHz) δ: 3.88 (s, 2H, CH2), 4.45 (s, 2H, CH2), 7.10–8.29 (m, 18H, Ar–H); 13C NMR (DMSO-d6) δ: 42.2(CH2), 46.6, (CH2), 121.5, 122.9, 126.0, 126.4, 127.0, 127.5, 128.3, 129.0, 129.3, 129.9, 130.2, 130.5, 131.0, 131.5, 132.1, 133.3, 139.1(CN2), 140.5(NCSe), 142.1, 144.1, 150.2, 160.0(CO); IR (KBr) v: 1990, 1674 and 1617 cm-1;MS (70 eV) m/z (%):533 (M+, 12). Anal. calcd. For C30H22N4OSe: C, 67.54; H, 4.16; N, 10.50; found C, 67.50; H, 4.11; N, 10.55.

2-(1-Oxo-4-(4-(pyridin-4-ylmethyl) phthalazin-2(1H)-yl)-N'-phenylacetimidoyl isoselenocyanate (5i)

M.p.88–89 ºC; yield 76%; 1H NMR (DMSO-d6) δ: 4.08 (s, 2H, CH2), 4.97 (s, 2H, CH2), 7.08–8.66 (m, 17H, Ar–H and pyridine protons); IR (KBr) v: 2015, 1679, 1616 cm-1; MS (70 eV) m/z (%):534 (M+, 15). Anal. calcd. For C29H21N5OSe: C, 65.17; H, 3.96; N, 13.10; found C, 65.10; H, 3.91; N, 13.16.

2-(1-Oxo-4-(biphenyl-4-yl) phthalazin-2(1H)-yl)-N'-phenylacetimidoyl isoselenocyanate (5j)

M.p.100–101 ºC; yield 66%; 1H NMR (DMSO-d6) δ: 3.80 (s, 2H, CH2), 7.04–8.29 (m, 18H, Ar–H); 13C NMR (DMSO-d6) δ: 46.6, (CH2), 121.4, 122.8,

125.2, 126.4, 126.9, 127.2, 127.5, 127.9, 128.2, 128.8, 129.3, 130.0, 130.6, 130.9, 132.5, 134.9, 138.1(CN2), 141.0(NCSe), 141.7, 142.1, 150.8, 161.1(CO); IR (KBr) v: 2009, 1677, 1612 cm-1; MS (70 eV) m/z (%):519 (M+, 7). Anal. calcd. For C29H20N4OSe: C, 67.05; H, 3.88; N, 10.79; found C, 67.10; H, 3.80; N, 10.77.

General procedure for preparation of N-(2-(1-oxo-4-substituted-phthalazin-2(1H)-yl)-1-(phenylamino) ethylidene) morpholine-4-carboselenoamide (6a-j)

To a stirred solution of 5, 1 equiv. of morpholine was added at room temperature. Te solution became orange immediately. After 10-40 min, 5 was completely consumed (TLC), and the solution was poured into water. In most of the cases, a yellow precipitate was formed during stirring for 1 h. when an emulsion was formed, the mixture was stirred for another few hours, and a small amount of MgSO4 was added to accelerate the precipitation. The solid was filtered by suction and air-dried.

N-(2-(1-Oxo-4-phenylphthalazin-2(1H)-yl)-1-(phenylamino) ethylidene) morpholine-4-carboselenoamide (6a)

M.p.110–111 ºC; yield 89%; 1H NMR (DMSO-d6) δ: 3.54 (s, 2H, CH2), 3.71, 3.82(2t, j=4.9 Hz, 2CH2N), 4.10, 4.32(2t, j=4.9 Hz, 2CH2O), 7.13–8.11 (m, 9H, Ar–H), 11.72 (s, 1H, NH exchangeable with D2O); 13C NMR (DMSO-d6) δ: 48.3 (CH2N), 50.2(CH2), 56.9(CH2N), 66.3 (CH2O), 66.7(CH2O), 116.0, 121.5, 123.2, 127.0, 127.4, 129.1, 129.5, 129.8, 131.6, 131.9, 132.9, 133.5, 134.8, 135.8, 140.2, 159.1(CN2), 160.0(CO), 184.6(CSe); IR (KBr) v: 3144, 1670 cm-1; MS (70 eV) m/z (%):532 (M+1, 34). Anal. calcd. For C27H25N5O2Se: C, 61.13; H, 4.75; N, 13.20; found C, 61.17; H, 4.70; N, 13.24.

N-(2-(1-Oxo-4-(4-methoxyphenyl) phthalazin-2(1H)-yl)-1-(phenylamino) ethylidene) morpholine-4-carboselenoamide (6b)

M.p.131–132 ºC; yield 70%; 1H NMR (DMSO-d6) δ: 3.54 (s, 2H, CH2), 3.67 (s, 3H, CH3), 3.75, 3.84(2t, j=4.9 Hz, 2CH2N), 4.12, 4.35(2t, j=4.9 Hz, 2CH2O), 7.10–8.14 (m, 8H, Ar–H), 12.01 (s, 1H, NH exchangeable with D2O); 13C NMR (DMSO-d6) δ: 48.3(CH2N), 52.1(CH2), 56.9 (CH2N), 58.8(OCH3), 66.3 (CH2O), 66.9(CH2O),116.3, 117.0, 122.0, 123.2, 125.3, 126.0, 128.0, 129.5, 130.4, 130.9, 131.8, 132.6, 135.3, 141.6, 159.7(CN2), 160.2(CO), 164.0, 184.8(CSe); IR (KBr) v: 3125, 1669 cm-1; MS (70 eV) m/z (%):560 (M+1, 18). Anal. calcd. For C28H27N5O3Se: C, 60.00; H, 4.86; N, 12.49; found C, 60.08; H, 4.83; N, 12.53.

N-(2-(1-Oxo-4-(4-chlorophenyl) phthalazin-2(1H)-yl)-1-(phenylamino) ethylidene) morpholine-4-carboselenoamide (6c)

M.p.126–127 ºC; yield 75%; 1H NMR (DMSO-d6) δ: 3.56 (s, 2H, CH2), 3.73, 3.84(2t, j=4.9 Hz, 2CH2N), 4.10, 4.34(2t, j=4.9 Hz, 2CH2O), 7.10–8.17 (m, 8H, Ar–H), 12.05 (s, 1H, NH exchangeable with D2O); 13C NMR (DMSO-d6) δ: 48.4 (CH2N), 54.1(CH2), 56.6(CH2N), 66.0 (CH2O), 66.3(CH2O), 115.1, 122.3, 123.0, 126.2, 127.9, 129.4, 129.9, 130.8, 131.7, 132.0, 132.9, 133.4, 135.4, 138.2, 141.0, 159.9(CN2), 161.2(CO), 185.2(CSe); IR (KBr) v: 3140, 1666 cm-1; MS (70 eV) m/z (%):565 (M+, 11). Anal. calcd. For C27H24ClN5O2Se: C, 57.40; H, 4.28; Cl, 6.28; N, 12.40; found C, 57.48; H, 4.22; Cl, 6.22; N, 12.43.

N-(2-(1-Oxo-4-(3, 4-dichlorophenyl) phthalazin-2(1H)-yl)-1-(phenylamino)ethylidene) morpholine-4-carboselenoamide (6d)

M.p.109–110 ºC; yield 77%; 1H NMR (DMSO-d6) δ: 3.51 (s, 2H, CH2), 3.70, 3.80(2t, j=4.9 Hz, 2CH2N), 4.12, 4.30(2t, j=4.9 Hz, 2CH2O), 7.11–8.07 (m, 7H, Ar–H), 11.92 (s, 1H, NH exchangeable with D2O); IR (KBr) v: 3132, 1666 cm-1; MS (70 eV) m/z (%):599 (M+, 13). Anal. calcd. For C27H23Cl2N5O2Se: C, 54.10; H, 3.87; Cl, 11.83; N, 11.68; found C, 54.10; H, 3.89; Cl, 11.83; N, 11.60.

N-(2-(1-Oxo-4-(4-(4-chlorobenzyl) phenyl) phthalazin-2(1H)-yl)-1-(phenylamino) ethylidene) morpholine-4-carboselenoamide (6e)

M.p.130–131 ºC; yield 82%; 1H NMR (DMSO-d6) δ: 3.52 (s, 2H, CH2), 3.74, 3.80(2t, j=4.9 Hz, 2CH2N), 3.95 (s, 2H, CH2), 4.11, 4.33(2t, j=4.9 Hz, 2CH2O), 7.09–8.21 (m, 12H, Ar–H), 12.11 (s, 1H, NH exchangeable with D2O); 13C NMR (DMSO-d6) δ: 42.6(CH2), 48.5 (CH2N), 53.1(CH2), 56.7(CH2N), 66.1 (CH2O), 66.7(CH2O), 116.0, 121.0, 123.2, 126.2, 128.0, 129.0, 129.5, 129.8, 130.2, 131.4, 131.8, 132.5, 132.9, 133.3, 134.5, 135.1, 140.2, 142.2, 144.7, 159.6(CN2), 161.2(CO), 184.9(CSe); IR (KBr) v: 3202, 1668 cm-1; MS (70 eV) m/z (%):655 (M+, 16). Anal. calcd. For C34H30ClN5O2Se: C, 62.34; H, 4.62; Cl, 5.41; N, 10.69; found C, 62.38; H, 4.60; Cl, 5.41; N, 10.72.

N-(2-(1-Oxo-4-(3-chloro-4-methylphenyl) phthalazin-2(1H)-yl)-1-(phenylamino) ethylidene) morpholine-4-carboselenoamide (6f)

M.p.143–144 ºC; yield 90%; 1H NMR (DMSO-d6) δ: 2.35 (s, 3H, CH3), 3.58 (s, 2H, CH2), 3.71, 3.81(2t, j=4.9 Hz, 2CH2N), 4.21, 4.37(2t, j=4.9 Hz, 2CH2O), 7.11–8.20 (m, 6H, Ar–H), 11.98 (s, 1H, NH exchangeable with D2O); IR (KBr) v: 3255, 1670 cm-1; MS (70 eV) m/z (%):578 (M+, 22). Anal. calcd. For C28H26ClN5O2Se: C, 58.09; H, 4.53; Cl, 6.12; N, 12.10; found C, 58.14; H, 4.58; Cl, 6.12; N, 12.15.

N-(2-(1-Oxo-4-(2, 4, 6-trimethylphenyl) phthalazin-2(1H)-yl)-1-(phenylamino) ethylidene) morpholine-4-carboselenoamide (6g)

M.p.127–128 ºC; yield 88%; 1H NMR (DMSO-d6) δ: 2.35 (s, 3H, CH3), 2.48 (s, 6H, 2CH3), 3.61 (s, 2H, CH2), 3.77, 3.85(2t, j=4.9 Hz, 2CH2N), 4.20, 4.37(2t, j=4.9 Hz, 2CH2O), 7.10–8.22 (m, 6H, Ar–H), 12.00 (s, 1H, NH exchangeable with D2O); 13C NMR (DMSO-d6) δ: 20.5(2CH3), 22.7(CH3), 48.0 (CH2N), 50.6(CH2), 56.5(CH2N), 66.6 (CH2O), 66.3(CH2O), 115.1, 122.7, 123.1, 126.4, 127.2, 129.0, 129.5, 129.9, 131.0, 131.5, 132.4, 135.6, 139.7, 141.0, 142.1, 159.6(CN2), 160.6(CO), 184.9(CSe); IR (KBr) v: 3250, 1678 cm-1; MS (70 eV) m/z (%):573 (M+1, 9). Anal. calcd. For C30H31N5O2Se: C, 62.93; H, 5.46; N, 12.23; found C, 62.90; H, 5.41; N, 12.20.

N-(2-(1-Oxo-4-(4-benzylphenyl) phthalazin-2(1H)-yl)-1-(phenylamino) ethylidene) morpholine-4-carboselenoamide (6h)

M.p.147–148 ºC; yield 72%; 1H NMR (DMSO-d6) δ: 3.50 (s, 2H, CH2), 3.71, 3.80(2t, j=4.9 Hz, 2CH2N), 3.91 (s, 2H, CH2), 4.12, 4.32(2t, j=4.9 Hz, 2CH2O), 7.08–8.29 (m, 13H, Ar–H), 11.71 (s, 1H, NH exchangeable with D2O); 13C NMR (DMSO-d6) δ: 44.1(CH2), 48.8 (CH2N), 53.1(CH2), 56.4(CH2N), 66.0 (CH2O), 66.9(CH2O), 116.5, 120.2, 124.2, 125.9, 126.4, 127.0, 129.0, 129.5, 129.8, 130.1, 130.8, 131.7, 132.6, 132.9, 133.5, 135.1, 142.8, 143.3, 145.1, 158.0(CN2), 160.3(CO), 184.6(CSe); IR (KBr) v: 3232, 1675 cm-1; MS (70 eV) m/z (%):620 (M+1, 30). Anal. calcd. For C34H31N5O2Se: C, 65.80; H, 5.03; N, 11.28; found C, 65.87; H, 5.00; N, 11.22.

N-(2-(1-Oxo-4-(4-(pyridin-4-ylmethyl) phthalazin-2(1H)-yl)-1-(phenylamino) ethylidene) morpholine-4-carboselenoamide (6i)

M.p.161–162 ºC; yield 71%; 1H NMR (DMSO-d6) δ: 3.52 (s, 2H, CH2), 3.77, 3.82(2t, j=4.9 Hz, 2CH2N), 3.97 (s, 2H, CH2), 4.15, 4.37(2t, j=4.9 Hz, 2CH2O), 7.11–8.55 (m, 12H, Ar–H and pyridine protons), 12.17 (s, 1H, NH exchangeable with D2O); IR (KBr) v: 3241, 1669 cm-1; MS (70 eV) m/z (%):621 (M+, 13). Anal. calcd. For C33H30N6O2Se: C, 63.76; H, 4.86; N, 13.52; found C, 63.79; H, 4.80; N, 13.49.

N-(2-(1-Oxo-4-(biphenyl-4-yl) phthalazin-2(1H)-yl)-1-(phenylamino) ethylidene) morpholine-4-carboselenoamide (6j)

M.p.159–160 ºC; yield 84%; 1H NMR (DMSO-d6) δ: 3.48 (s, 2H, CH2), 3.70, 3.80(2t, j=4.9 Hz, 2CH2N), 4.11, 4.32(2t, j=4.9 Hz, 2CH2O), 7.10–8.28 (m, 13H, Ar–H), 12.10 (s, 1H, NH exchangeable with D2O); 13C NMR (DMSO-d6) δ: 49.0 (CH2N), 52.1(CH2), 56.4(CH2N), 67.1 (CH2O), 66.9(CH2O), 115.7, 120.9, 123.1, 127.0, 128.2, 128.7, 129.3, 129.6, 129.9, 130.1, 130.9, 131.4, 132.6, 133.7, 134.3, 136.2, 141.3, 142.7, 144.7, 158.7(CN2), 159.8(CO), 184.6(CSe); IR (KBr) v: 3232, 1675 cm-1; MS (70 eV) m/z (%):607 (M+1, 67). Anal. calcd. For C33H29N5O2Se: C, 65.34; H, 4.82; N, 11.55; found C, 65.30; H, 4.87; N, 11.50.

General procedure for preparation of ethyl 2-morpholino-4-((1-oxo-4-substituted-phthalazin-2(1H)-yl) methyl)-1, 3-selenazole-5-carboxylate (8a-j)

To a stirred solution of 6 in acetone, 1 equiv. of ethylbromoacetate was added at room temperature. Within a few minutes, iminium salt was precipitated. The mixture was concentrated i.v., and the precipitate was filtered. The solid was suspended in acetone, and 1.1-1.3 equiv. of Et3N was added. After a few minutes, a clear solution was formed, and then a solid precipitated. After stirring for 20-40 min., the mixture was poured into ice-water, and stirred for another 40 min. to 1.5 h. the precipitate was filtered by suction and air-dried.

Ethyl 2-morpholino-4-((1-oxo-4-phenylphthalazin-2(1H)-yl) methyl)-1, 3-selenazole-5-carboxylate (8a)

M.p.218–219 ºC; yield 91%; 1H NMR (DMSO-d6) δ: 1.21 (t, j = 7.1 Hz, 3H, CH3CH2), 3.51(t, j=4.9 Hz, 2CH2N), 3.80(t, j=4.9 Hz, 2CH2O), 4.02 (s, 2H, CH2), 4.70 (q, j = 7.1 Hz, 2H, CH2CH3), 7.12–8.10 (m, 9H, Ar–H); 13C NMR (DMSO-d6) δ: 14.5(CH3), 49.9(2CH2N), 60.6(CH2 of ester), 63.4(CH2), 66.0(2CH2O), 115.2(C5), 123.8, 127.0, 127.9, 129.1, 129.5, 131.3, 131.6, 132.6, 133.1, 134.3, 135.0, 160.3(CO), 160.9 (C4), 165.1(COO), 173.7 (C2); IR (KBr) v: 1732 and 1676 cm-1; MS (70 eV) m/z (%):524 (M+1, 100). Anal. calcd. For C25H24N4O4Se: C, 57.36; H, 4.62; N, 10.70; found C, 57.40; H, 4.66; N, 10.73.

Ethyl 2-morpholino-4-((1-oxo-4-(4-methoxyphenyl) phthalazin-2(1H)-yl) methyl)-1, 3-selenazole-5-carboxylate (8b)

M.p.199–200 ºC; yield 93%; 1H NMR (DMSO-d6) δ: 1.20 (t, j = 7.1 Hz, 3H, CH3CH2), 3.54(t, j=4.9 Hz, 2CH2N), 3.86(t, j=4.9 Hz, 2CH2O), 4.07 (s, 2H, CH2), 4.15 (s, 3H, OCH3), 4.79 (q, j = 7.1 Hz, 2H, CH2CH3), 7.10–8.14 (m, 8H, Ar–H); 13C NMR (DMSO-d6) δ: 14.9(CH3), 50.0(2CH2N), 57.0(OCH3), 60.4(CH2 of ester), 63.5(CH2), 66.9(2CH2O), 117.0(C5), 118.3, 123.9, 125.4, 126.2, 127.6, 130.3, 130.9, 131.8, 133.0, 135.0, 154.0(C4), 159.2(CO), 164.5, 165.0(COO), 173.9 (C2); IR (KBr) v: 1735, 1676 and 1605 cm-1; MS (70 eV) m/z (%):554 (M+1, 10). Anal. calcd. For C26H26N4O5Se: C, 56.42; H, 4.73; N, 10.12; found C, 56.48; H, 4.70; N, 10.10.

Ethyl 2-morpholino-4-((1-oxo-4-(4-chlorophenyl) phthalazin-2(1H)-yl) methyl)-1, 3-selenazole-5-carboxylate (8c)

M.p.208–209 ºC; yield 88%; 1H NMR (DMSO-d6) δ: 1.26 (t, j = 7.1 Hz, 3H, CH3CH2), 3.54(t, j=4.9 Hz, 2CH2N), 3.862(t, j=4.9 Hz, 2CH2O), 4.19 (s, 2H, CH2), 4.82 (q, j = 7.1 Hz, 2H, CH2CH3),7.20–8.18 (m, 8H, Ar–H); 13C NMR (DMSO-d6) δ: 14.9(CH3), 49.5(2CH2N), 60.0(CH2 of ester), 63.1(CH2), 67.3(2CH2O), 117.8(C5), 123.2, 126.5, 127.5, 129.3, 130.5, 131.5, 132.6, 132.9, 133.6, 135.1, 138.3, 159.1(C4), 160.4(CO), 165.0(COO), 172.0 (C2); IR (KBr) v: 1739, 1678 and 1609 cm-1; MS (70 eV) m/z (%):557 (M+, 21). Anal. calcd. For C25H23ClN4O4Se: C, 53.82; H, 4.16; Cl, 6.35; N, 10.04; found C, 53.88; H, 4.17; Cl, 6.30; N, 10.09.

Ethyl 2-morpholino-4-((1-oxo-4-(3, 4-dichlorophenyl) phthalazin-2(1H)-yl) methyl)-1, 3-selenazole-5-carboxylate (8d)

M.p.188–189 ºC; yield 90%; 1H NMR (DMSO-d6) δ: 1.30 (t, j = 7.1 Hz, 3H, CH3CH2), 3.55(t, j=4.9 Hz, 2CH2N), 3.85(t, j=4.9 Hz, 2CH2O), 4.12 (s, 2H, CH2), 5.01 (q, j = 7.1 Hz, 2H, CH2CH3),7.22–8.27 (m, 7H, Ar–H); IR (KBr) v: 1744, 1679 and 1607 cm-1; MS (70 eV) m/z (%):592 (M+, 16). Anal. calcd. For C25H22Cl2N4O4Se: C, 50.69; H, 3.74; Cl, 11.97; N, 9.46; found C, 50.76; H, 3.79; Cl, 11.92; N, 9.41.

Ethyl 2-morpholino-4-((1-oxo-4-(4-(4-chlorobenzyl) phthalazin-2(1H)-yl) methyl)-1, 3-selenazole-5-carboxylate (8e)

M.p.225–226 ºC; yield 93%; 1H NMR (DMSO-d6) δ: 1.26 (t, j = 7.1 Hz, 3H, CH3CH2), 3.54(t, j=4.9 Hz, 2CH2N), 3.82(t, j=4.9 Hz, 2CH2O), 4.07 (s, 2H, CH2), 4.27 (s, 2H, CH2), 4.89 (q, j = 7.1 Hz, 2H, CH2CH3), 7.12–8.24 (m, 12H, Ar–H); 13C NMR (DMSO-d6) δ: 14.3(CH3), 42.4(CH2), 49.1(2CH2N), 60.6(CH2 of ester), 63.1(CH2), 65.8(2CH2O), 116.2(C5), 123.2, 126.4, 128.3, 129.1, 129.7, 130.5, 131.8, 132.2, 132.9, 133.3, 133.9, 134.8, 135.4, 140.7, 144.1, 159.8(C4), 160.8(CO), 165.0(COO), 174.4 (C2), IR (KBr) v: 1739, 1678 and 1608 cm-1; MS (70 eV) m/z (%):648 (M+, 9). Anal. calcd. For C32H29ClN4O4Se: C, 59.31; H, 4.51; Cl, 5.47; N, 8.65; found C, 59.27; H, 4.50; Cl, 5.47; N, 8.63.

Ethyl 2-morpholino-4-((1-oxo-4-(3-chloro-4-methylphenyl) phthalazin-2(1H)-yl) methyl)-1, 3-selenazole-5-carboxylate (8f)

M.p.213–214 ºC; yield 95%; 1H NMR (DMSO-d6) δ: 1.24 (t, j = 7.1 Hz, 3H, CH3CH2), 2.47 (s, 3H, CH3), 3.55(t, j=4.9 Hz, 2CH2N), 3.80(t, j=4.9 Hz, 2CH2O), 4.05 (s, 2H, CH2), 4.88 (q, j = 7.1 Hz, 2H, CH2CH3), 7.14–8.10 (m, 7H, Ar–H); IR (KBr) v: 1743, 1678 and 1605 cm-1; MS (70 eV) m/z (%):572 (M+, 19). Anal. calcd. For C26H25ClN4O4Se: C, 54.60; H, 4.41; Cl, 6.20; N, 9.80; found C, 54.68; H, 4.43; Cl, 6.20; N, 9.77.

Ethyl 2-morpholino-4-((1-oxo-4-(2, 4, 6-trimethylphenyl) phthalazin-2(1H)-yl) methyl)-1, 3-selenazole-5-carboxylate (8g)

M.p.180–181 ºC; yield 89%; 1H NMR (DMSO-d6) δ: 1.22 (t, j = 7.1 Hz, 3H, CH3CH2), 2.40 (s, 3H, CH3), 2.48 (s, 6H, 2CH3), 3.53(t, j=4.9 Hz, 2CH2N), 3.85(t, j=4.9 Hz, 2CH2O), 4.06 (s, 2H, CH2), 4.88 (q, j = 7.1 Hz, 2H, CH2CH3), 7.10–8.11 (m, 6H, Ar–H); 13C NMR (DMSO-d6) δ: 15.4(CH3), 20.6(2CH3), 22.9(CH3), 49.0(2CH2N), 59.2(CH2 of ester), 64.3(CH2), 66.7(2CH2O), 117.3(C5), 123.0, 126.2, 127.5, 129.1, 130.0, 131.4, 131.9, 132.3, 135.3, 139.0, 141.7, 158.8(C4), 159.6(CO), 165.0(COO), 172.1 (C2); IR (KBr) v: 1741, 1677 and 1609 cm-1; MS (70 eV) m/z (%):566 (M+1, 10). Anal. calcd. for C28H30N4O4Se: C, 59.47; H, 5.35; N, 9.91; found C, 59.44; H, 5.38; N, 9.90.

Ethyl 2-morpholino-4-((1-oxo-4-(4-benzylphenyl) phthalazin-2(1H)-yl) methyl)-1, 3-selenazole-5-carboxylate (8h)

M.p.231–232 ºC; yield 94%; 1H NMR (DMSO-d6) δ: 1.25 (t, j = 7.1 Hz, 3H, CH3CH2), 3.54(t, j=4.9 Hz, 2CH2N), 3.81(t, j=4.9 Hz, 2CH2O), 4.05 (s, 2H, CH2), 4.25 (s, 2H, CH2), 4.90 (q, j = 7.1 Hz, 2H, CH2CH3), 7.11–8.19 (m, 13H, Ar–H); 13C NMR (DMSO-d6) δ: 14.0(CH3), 43.8(CH2), 49.7(2CH2N), 61.1(CH2 of ester), 64.0(CH2), 65.1(2CH2O), 115.2(C5), 124.1, 126.3, 126.8, 127.7, 129.2, 129.7, 130.0, 130.7, 131.5, 132.2, 132.8, 134.2, 135.2, 142.5, 145.3, 158.9(C4), 159.7(CO), 164.1(COO), 174.1 (C2); IR (KBr) v: 1739, 1676 and 1607 cm-1; MS (70 eV) m/z (%):613 (M+, 7). Anal. calcd. For C32H30N4O4Se: C, 62.64; H, 4.93; N, 9.13; O, 10.43; found C, 62.60; H, 4.91; N, 9.22; O, 10.42.

Ethyl 2-morpholino-4-((1-oxo-4-(4-(pyridin-4-ylmethyl) phthalazin-2(1H)-yl) methyl)-1, 3-selenazole-5-carboxylate (8i)

M.p.265–266 ºC; yield 90%; 1H NMR (DMSO-d6) δ: 1.26 (t, j = 7.1 Hz, 3H, CH3CH2), 3.56(t, j=4.9 Hz, 2CH2N), 3.84(t, j=4.9 Hz, 2CH2O), 4.09 (s, 2H, CH2), 4.18 (s, 2H, CH2), 4.81 (q, j = 7.1 Hz, 2H, CH2CH3), 7.14–8.69 (m, 12H, Ar–H and pyridine protons); IR (KBr) v: 1738, 1676 and 1607 cm-1; MS (70 eV) m/z (%):615 (M+1, 100). Anal. calcd. For C31H29N5O4Se: C, 60.59; H, 4.76; N, 11.40; found C, 60.51; H, 4.70; N, 11.44.

Ethyl 2-morpholino-4-((1-oxo-4-(biphenyl-4-yl) phthalazin-2(1H)-yl) methyl)-1, 3-selenazole-5-carboxylate (8j)

M.p.242–243 ºC; yield 87%; 1H NMR (DMSO-d6) δ: 1.26 (t, j = 7.1 Hz, 3H, CH3CH2), 3.55(t, j=4.9 Hz, 2CH2N), 3.83(t, j=4.9 Hz, 2CH2O), 4.11 (s, 2H, CH2), 4.81 (q, j = 7.1 Hz, 2H, CH2CH3), 7.13–8.16 (m, 13H, Ar–H); 13C NMR (DMSO-d6) δ:

14.2(CH3), 50.3(2CH2N), 61.6(CH2 of ester), 63.2(CH2), 66.5(2CH2O), 115.5(C5), 123.2, 127.4, 128.1, 128.7, 129.1, 129.7, 130.1, 130.8, 131.8, 132.5, 133.0, 134.7, 135.2, 141.0, 144.4, 158.1(C4), 160.8(CO), 163.2(COO), 173.0 (C2); IR (KBr) v: 1733, 1675 and 1606 cm-1; MS (70 eV) m/z (%):600 (M+1, 25). Anal. calcd. For C31H28N4O4Se: C, 62.10; H, 4.71; N, 9.34; found C, 62.04; H, 4.75; N, 9.34.

General procedure for preparation of 2-((2-morpholino-1, 3-selenazol-4-yl) methyl)-4-substituted-phthalazin-1(2H)-one (9a-j)

To a solution of ethyl 1, 3-selenazole-5-carboxylate in acetone, an aqueous solution of NaOH (5%) was added (2-3 equiv. of NaOH). Then, acetonewas added to obtain a homogenous solution, and the mixture was heated under reflux. After 2h, the starting material was consumed (TLC), the mixture was poured into ice-water, and the product was isolated by filtration.

2-((2-Morpholino-1, 3-selenazol-4-yl) methyl)-4-phenylphthalazin-1(2H)-one (9a).

M.p.101–102 ºC; yield 72%; 1H NMR (DMSO-d6) δ: 3.52(t, j=4.9 Hz, 2CH2N), 3.81(t, j=4.9 Hz, 2CH2O), 4.01 (s, 2H, CH2), 7.01(s, 1H, CH of selenazole moiety), 7.15–8.10 (m, 9H, Ar–H); 13C NMR (DMSO-d6) δ: 49.7(2CH2N), 63.1(CH2), 66.3(2CH2O), 106.1(C5), 123.9, 127.0, 127.8, 129.0, 129.6, 131.3, 131.9, 132.6, 133.4, 134.2, 135.1, 153.3(C4), 160.3(CO), 173.0 (C2); IR (KBr) v: 1731 and 1679 cm-1; MS (70 eV) m/z (%):451 (M+, 14). Anal. calcd. For C22H20N4O2Se: C, 58.54; H, 4.47; N, 12.41; found C, 58.59; H, 4.42; N, 12.41.

2-((2-Morpholino-1, 3-selenazol-4-yl) methyl)-4-(4-methoxyphenyl) phthalazin-1(2H)-one (9b).

M.p.112–113 ºC; yield 72%; 1H NMR (DMSO-d6) δ: 3.53(t, j=4.9 Hz, 2CH2N), 3.82(t, j=4.9 Hz, 2CH2O), 4.02 (s, 2H, CH2), 4.13 (s, 3H, OCH3), 7.02(s, 1H, CH of selenazole moiety), 7.10–8.11 (m, 8H, Ar–H); 13C NMR (DMSO-d6) δ: 50.1(2CH2N), 57.2(OCH3), 63.7(CH2), 66.9(2CH2O), 107.0(C5), 116.1, 123.8, 125.6, 126.0, 127.6, 130.1, 130.9, 131.7, 132.9, 135.2, 153.8(C4), 160.7(CO), 164.5, 173.9 (C2); IR (KBr) v: 1670 and 1606 cm-1; MS (70 eV) m/z (%):482 (M+1, 9). Anal. calcd. For C23H22N4O3Se: C, 57.38; H, 4.61; N, 11.64; found C, 57.30; H, 4.55; N, 11.66.

2-((2-Morpholino-1, 3-selenazol-4-yl) methyl)-4-(4-chlorophenyl) phthalazin-1(2H)-one (9c).

M.p.107–108 ºC; yield 69%; 1H NMR (DMSO-d6) δ: 3.55(t, j=4.9 Hz, 2CH2N), 3.82(t, j=4.9 Hz, 2CH2O), 4.10 (s, 2H, CH2), 7.06(s, 1H, CH of selenazole moiety), 7.21–8.14 (m, 8H, Ar–H); 13C NMR (DMSO-d6) δ: 49.8(2CH2N), 63.0(CH2), 67.1(2CH2O), 106.8(C5), 123.5, 126.8, 127.7, 129.1, 130.5, 131.4, 132.4, 132.9, 133.2, 135.0, 138.1, 154.0(C4), 160.4(CO), 173.2 (C2); IR (KBr) v: 1673 and 1607 cm-1. Anal. calcd. For C22H19ClN4O2Se: C, 54.39; H, 3.94; Cl, 7.30; N, 11.53; found C, 54.44; H, 3.91; Cl, 7.30; N, 11.55.

2-((2-Morpholino-1, 3-selenazol-4-yl) methyl)-4-(3, 4-dichlorophenyl) phthalazin-1(2H)-one (9d).

M.p.90–91 ºC; yield 77%; 1H NMR (DMSO-d6) δ: 3.54(t, j=4.9 Hz, 2CH2N), 3.83(t, j=4.9 Hz, 2CH2O), 4.07 (s, 2H, CH2), 7.04(s, 1H, CH of selenazole moiety), 7.33–8.21 (m, 7H, Ar–H); IR (KBr) v: 1676 and 1609 cm-1; MS (70 eV) m/z (%):521 (M+1, 15). Anal. calcd. For C22H18Cl2N4O2Se: C, 50.79; H, 3.49; Cl, 13.63; N, 10.77; found C, 50.83; H, 3.54; Cl, 13.60; N, 10.74.

2-((2-Morpholino-1, 3-selenazol-4-yl) methyl)-4-(4-(4-chlorobenzyl) phthalazin-1(2H)-one (9e).

M.p.124–125 oC; yield 74%; 1H NMR (DMSO-d6) δ: 3.53(t, j=4.9 Hz, 2CH2N), 3.80(t, j=4.9 Hz, 2CH2O), 4.04 (s, 2H, CH2), 4.22 (s, 2H, CH2), 7.01(s, 1H, CH of selenazole moiety), 7.13–8.21 (m, 12H, Ar–H); 13C NMR (DMSO-d6) δ: 42.1(CH2), 49.5(2CH2N), 63.1(CH2), 66.7(2CH2O), 107.0(C5), 123.0, 126.4, 128.0, 129.1, 129.3, 130.1, 131.4, 131.9, 132.3, 132.9, 133.7, 134.3, 135.1, 140.0, 144.1, 154.4(C4), 160.8(CO), 173.0 (C2), IR (KBr) v: 1675 and 1602 cm-1; MS (70 eV) m/z (%):576 (M+, 12). Anal. calcd. For C29H25ClN4O2Se: C, 60.48; H, 4.38; Cl, 6.16; N, 9.73; found C, 60.42; H, 4.41; Cl, 6.16; N, 9.71.

2-((2-Morpholino-1, 3-selenazol-4-yl) methyl)-4-(3-chloro-4-methylphenyl) phthalazin-1(2H)-one (9f).

M.p.117–118 ºC; yield 70%; 1H NMR (DMSO-d6) δ: 2.43 (s, 3H, CH3), 3.57(t, j=4.9 Hz, 2CH2N), 3.83(t, j=4.9 Hz, 2CH2O), 4.10 (s, 2H, CH2), 7.00(s, 1H, CH of selenazole moiety), 7.16–8.10 (m, 7H, Ar–H); IR (KBr) v: 1676 and 1607 cm-1. Anal. calcd. For C23H21ClN4O2Se: C, 55.27; H, 4.23; Cl, 7.09; N, 11.21; found C, 55.32; H, 4.20; Cl, 7.09; N, 11.26.

2-((2-Morpholino-1, 3-selenazol-4-yl) methyl)-4-(2, 4, 6-trimethylphenyl) phthalazin-1(2H)-one (9g).

M.p.103–104 ºC; yield 80%; 1H NMR (DMSO-d6, 300 MHz) δ: 2.42 (s, 3H, CH3), 2.50 (s, 6H, 2CH3), 3.51(t, j=4.9 Hz, 2CH2N), 3.80(t, j=4.9 Hz, 2CH2O), 4.01 (s, 2H, CH2), 7.01(s, 1H, CH of selenazole moiety), 7.12–8.04 (m, 6H, Ar–H); 13C NMR (DMSO-d6) δ: 20.1(2CH3), 22.5(CH3), 49.5(2CH2N), 63.0(CH2), 66.2(2CH2O), 106.0(C5), 123.5, 126.1, 127.9, 129.2, 129.9, 131.3, 131.9, 132.9, 135.3, 139.2, 141.7, 153.4(C4), 160.1(CO), 172.6 (C2); IR (KBr) v: 1670 and 1607 cm-1; MS (70 eV) m/z (%):493 (M+, 11). Anal. calcd. For C25H26N4O2Se: C, 60.85; H, 5.31; N, 11.35; found C, 60.88; H, 5.27; N, 11.38.

2-((2-Morpholino-1, 3-selenazol-4-yl) methyl)-4-(4-benzylphenyl) phthalazin-1(2H)-one (9h).
M.p.133–134 ºC; yield 78%; 1H NMR (DMSO-d6) δ: 3.53(t, j=4.9 Hz, 2CH2N), 3.81(t, j=4.9 Hz, 2CH2O), 4.01 (s, 2H, CH2), 4.21 (s, 2H, CH2), 7.02(s, 1H, CH of selenazole moiety), 7.10–8.15 (m, 13H, Ar–H); 13C NMR (DMSO-d6) δ: 43.5(CH2), 49.0(2CH2N), 64.1(CH2), 65.7(2CH2O), 106.6(C5), 124.0, 126.1, 126.8, 127.3, 129.0, 129.7, 130.0, 130.6, 131.7, 132.2, 132.9, 133.8, 135.1, 142.2, 145.0, 154.0(C4), 159.1(CO), 172.9 (C2); IR (KBr) v: 1674 and 1606 cm-1; MS (70 eV) m/z (%):542 (M+1, 7). Anal. calcd. For C29H26N4O2Se: C, 64.32; H, 4.84; N, 10.35; found C, 64.38; H, 4.81; N, 10.30.

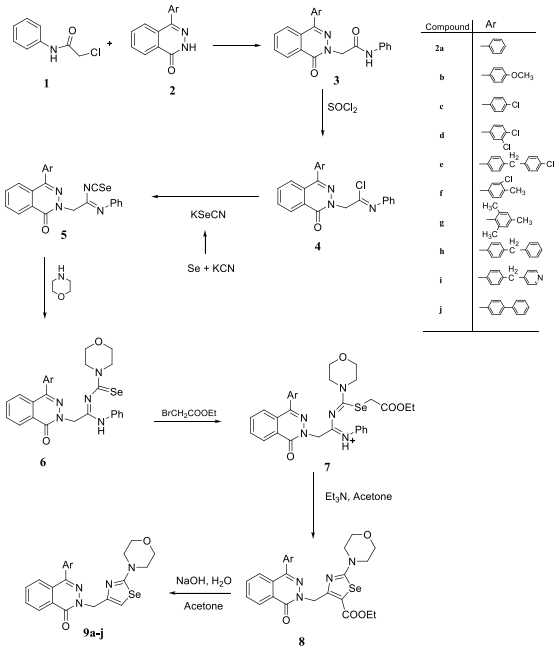
2-((2-Morpholino-1, 3-selenazol-4-yl) methyl)-4-(4-(pyridin-4-ylmethyl) phthalazin-1(2H)-one (9i).
M.p.143–144 ºC; yield 70%; 1H NMR (DMSO-d6) δ: 3.56(t, j=4.9 Hz, 2CH2N), 3.83(t, j=4.9 Hz, 2CH2O), 4.05 (s, 2H, CH2), 4.16 (s, 2H, CH2), 7.03(s, 1H, CH of selenazole moiety), 7.12–8.65 (m, 12H, Ar–H and pyridine protons); IR (KBr) v: 1675 and 1608 cm-1; MS (70 eV) m/z (%):542 (M+, 18). Anal. calcd. For C28H25N5O2Se: C, 61.99; H, 4.64; N, 12.91; found C, 62.07; H, 4.60; N, 12.98.

2-((2-Morpholino-1, 3-selenazol-4-yl) methyl)-4-(biphenyl-4-yl) phthalazin-1(2H)-one (9j).
M.p.146–147 ºC; yield 77%; 1H NMR (DMSO-d6) δ: 3.54(t, j=4.9 Hz, 2CH2N), 3.81(t, j=4.9 Hz, 2CH2O), 3.98 (s, 2H, CH2), 7.00(s, 1H, CH of selenazole moiety), 7.13–8.10 (m, 13H, Ar–H); 13C NMR (DMSO-d6) δ: 50.0(2CH2N), 63.9(CH2), 66.7(2CH2O), 107.1(C5), 123.9, 127.1, 128.0, 128.7, 129.0, 129.6, 130.3, 130.9, 131.8, 132.6, 133.7, 134.5, 135.0, 141.1, 144.2, 153.2(C4), 159.8(CO), 173.7 (C2); IR (KBr) v: 1677 and 1608 cm-1; MS (70 eV) m/z (%):528 (M+1, 10). Anal. calcd. For C28H24N4O2Se: C, 63.76; H, 4.59; N, 10.62; found C, 63.79; H, 4.53; N, 10.67.

3. Results and Discussion

3.1. Synthesis

Phthalazin-1(2H)-one 2 were treated with 2-chloro-N-phenylacetamide in refluxing acetone to afford the corresponding N-phenylacetamide derivative 3a-j. The structure of compounds 3a-j was confirmed based on their elemental analysis and spectral data. The IR spectrum showed a characteristic absorption band at ν = 1697-1680 and 1658-1650 cm-1 corresponding to 2 CO groups. The 1HNMR spectrum of 3a-j showed NH at δ = 7.90-8.11 ppm. The reaction of N-phenylacetamide of type 3 with excess SOCl2 under reflux gave N-phenylacetimidoyl chlorides 4, which on treatment with KeSeCN in acetone yielded imidoyl isoselenocyanates of type 5. The IR spectrum of 5a-j showed an absorption band at 1980-2050 cm−1 assigned to the isoselenocyanate structure as was the singlet at 136-140.3 ppm in the 13CNMR spectrum. Furthermore, the compound showed correct elemental analysis and intense peak for molecular ion. The imidoyl isoselenocyanates of type 5 were transformed into selenourea derivatives 6 by the reaction with morpholine. In acetone at room temperature, 6 reacted with activated bromomethylene compounds such as ethylbromoacetate, phenacyl bromides and 4-cyanobenzyl bromides, to give 1, 3-selenazol-2-amines of type 8. A reaction mechanism via alkylation of Se-atom of 6, followed by ring closure and elimination of anilines, is most likely [23]. 1, 3-selenazoles of type 8, after saponification with 5% NaOH solution under reflux, de-esterification smoothly to give the corresponding 1, 3-selenazoles 9a-j. (Scheme 1):



Scheme 1. Synthesis of phthalazine selenazole derivatives 9 (a-j)

3.2. Biological activities

Disk diffusion method was used in order to determine the antimicrobial activity of the newly synthesized compounds 8a-j and 9a-j. Different species of microorganisms (Bacteria and fungi) were selected in this test that are: Escherichia coli, Staphylococcus aureus, Bacillus subtilis, Salmonella typhi, Aspergillums niger and Candida albicans. Amoxicillin and Ketoconazole were used as standard drugs control for both bacteria and fungi, respectively. Preliminary test of phthalazine-derivatives together with the standard drugs was

proceeded at concentration of 500 µg/mL. The obtained inhibition zones for all samples were measured after 24h for bacteria and after 72h in case of fungi. Each test was repeated twice. Based on the obtained previous results, the minimum inhibitory concentration (MIC) for all these compounds; 8a-j and 9a-j was determined by the liquid dilution method against both types; bacterial and fungi. According to the previous work [24]: "Stock solutions of the tested compounds of concentrations: 500, 250, 200, 100, 62.5, 50, 25 and 12.5 µg mL^{-1}, were all dissolved in DMSO as solvent". "The solutions of standard drugs, Amoxicillin and Ketoconazole, were also prepared using the same concentrations" [24]. "Inoculums of both bacterial and fungal were also prepared. "To a series of tubes containing 1 mL of phthalazine compound, solution with different concentrations and 0.2 mL of the inoculums was added" [24]. "Later, 3.8 mL of sterile water was added to each of the test tubes then, all tubes were incubated for 24h at 37ºC ". The previous method was repeated by changing phthalazine compounds together with the standard drugs; Amoxicillin and Ketoconazole for comparison [24]. The MIC was determined (**Table 1**) where the comparison of MICs (in µg/mL) of both potent compounds and standard drugs against tested organisms are presented.

Table 1. Antimicrobial activity of compounds 8a-j and 9a-j

Compounds	Minimum inhibitory concentration (MIC) in µg/mL					
	Bacterial strains				Fungal strains	
	S. aureus	*B. subtilis*	*S. typhi*	*E. coli*	*A. niger*	*C. albican*
8a	250	200	200	250	500	250
8b	200	100	200	250	500	-
8c	25	50	50	100	125	62.5
8d	25	50	25	50	62.5	125
8e	25	25	25	25	62.5	62.5
8f	25	50	25	50	125	62.5
8g	100	50	50	50	62.5	125
8h	500	250	-	250	500	-
8i	25	25	50	50	62.5	125
8j	500	200	250	-	500	125
9a	500	250	100	100	-	250
9b	25	100	50	50	125	62.5
9c	50	25	25	25	125	62.5
9d	25	12.5	12.5	12.5	62.5	62.5
9e	12.5	12.5	12.5	12.5	62.5	62.5
9f	25	25	12.5	50	62.5	125
9g	25	25	25	12.5	62.5	62.5
9h	100	100	250	50	250	-
9i	25	12.5	25	12.5	62.5	62.5
9j	500	250	100	250	125	250
Amoxicillin	62.5	62.5	62.5	62.5	-	-
Ketaconazole	-	-	-	-	31.25	31.25

Conclusion

Two series of new compounds derived from 1, 3-selenazole and phthalazin-1-(2H)-one are designed and prepared. The compounds of the first series containing ester groups (-COOC2H5) were de-esterificated with 5% of sodium hydroxide to obtain the second series. The antibacterial and antifungal investigation against particular species of bacteria and fungi was performed for both series. Based on the results of this study achieved, all prepared compounds exhibit biological activities. The presence or absence of the ester group does not significantly affect the biological activities. However, a remarkable increase of activities against both bacteria and fungi was observed for two compounds of the second series (9e and 9i). The lowest MIC value (12.5 µg/mL and 62.5 µg/mL) was achieved for the compound 9e, when investigated against all species of bacteria tested and both fungi studied respectively. A similar MIC values were obtained for compound 9i. Thus, in comparison with the other derivatives, the MIC values of these two compounds are almost 2-40-times lower and only 2 times higher than the MIC values of the standard drugs (Amoxicillin and Ketoconazole).

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